SOLUBLE ESTRADIOL CAPSULE FOR VAGINAL INSERTION

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a nonprovisional application of and claims priority to the following: U.S. Provisional Patent Application No. 61/745,313, entitled "SOLUBLE ESTRADIOL CAPSULE FOR VAGINAL INSERTION," which was filed on Dec. 21, 2012, All aforementioned applications are hereby incorporated by reference herein in their entirety.

BACKGROUND

Field

Postmenopausal women frequently suffer from certain vaginally localized states including, for example, atrophic vaginitis or vulvar and vaginal atrophy (hereinafter "vulvovaginal atrophy" or "VVA") with symptoms including, for example, dryness, itching, soreness, irritation, bleeding and dyspareunia; with urinary frequency, urgency, urinary discomfort and incontinence also occurring (singularly and collectively, "estrogen-deficient urinary state(s)"). For the sake of clarity, the terms "atrophic vaginitis" and vulvovaginal atrophy are used herein interchangeably. The molecular morphology of VVA is well known in the medical field.

Each of these WA-related states, inter alia, are symptoms associated with decreased estrogenization of the vulvovaginal tissue, and can even occur in women treated with oral administration of an estrogen-based pharmaceutical drug product. Although WA is most common with menopausal women, it can occur at any time in a woman's life cycle.

WA-related states are generally treated with local administration of an estrogen-based natural or synthetic hormone in the form of a topically applied gel or cream, or through vaginal insertion of a compressed tablet. These forms of administration can provide low levels of circulating estrogen but are not intended to contribute to the treatment of other states related to estrogen deficiencies typically treated via administration of a systemically absorbed estrogen product. For example, such systemically absorbed products include orally administered formulations as well as creams, gels, sprays, and transdermally delivered products. However, vaginal gels and creams may rub, wear or wash off before the estrogen is fully absorbed into the local tissue. In addition, various commercially available estrogen-containing creams contain an alcohol such as benzyl alcohol and/or stearyl alcohol. The use of such products may result in itching or burning when applied. The above referenced vaginal creams and gels require insertion via a reusable vaginal applicator/plunger for which patients complain of difficulty to accurately dose, discomfort or pain upon insertion, and increased trauma to the genital mucosa all in relation to the vaginal applicator. Furthermore, the reusable applicator/plunger is also difficult to clean resulting in hygienic concerns as well as increased rates of infection all decreasing the ongoing compliance of the therapy.

Similarly, vaginal suppositories in the form of inserted tablets may not fully dissolve, reducing the effective dose of absorbed estrogen; may cause unwanted and unnecessary vaginal discharge; may cause an increase of vulvovaginal pruritus and/or back pain; and the insertion, itself, using the applicator provided with the reference-listed tableted drug, VAGIFEM® (estradiol vaginal tablet, Novo Nordisk; Princeton, NJ), may cause a rupture of the vaginal fornix.

There has been at least one attempt at providing a soluble or suspended estrogen capsule for vaginal insertion as described in U.S. Pat. No. 6,060,077 (the '077 patent). The '077 patent provides for a non-systemic treatment for vaginal dryness in menopausal women using an immediate or slow-release formulation comprising a natural estrogen compound in solution or suspension in a lipophilic agent, a hydrophilic gel-forming bioadhesive agent, a gelling agent for the lipophilic agent, and a hydrodispersible agent in a hard or soft capsule. It is specifically stated that these formulations are designed to avoid systemic passage of estradiol following administration. Once in contact with vaginal secretions, these formulations require the presence of the hydrophilic gel-forming bioadhesive agent to react with the hydrodispersible agent to form an estrogen-containing emulsion to facilitate absorption. A practical issue arises when attempting to use this medicament when vaginal secretions are required to activate the formulation while the treatment is designed to treat vaginal dryness.

Accordingly, an estrogen-based vaginal suppository that provides an ease of administration/insertion, improved safety of insertion, lacking or minimizing vaginal discharge following administration, and that does not require vaginal secretions to activate the formulation could provide a more effective dosage form with improved efficacy, safety and patient compliance.

SUMMARY

According to various embodiments of this disclosure, encapsulated pharmaceutical formulations comprising solubilized estradiol are provided. Such formulations are encapsulated in soft capsules which are vaginally inserted for the treatment of vulvovaginal atrophy.

BRIEF DESCRIPTION OF THE DRAWINGS

The subject matter of the present invention is particularly pointed out and distinctly claimed in the concluding portion of the specification. A more complete understanding of the present invention, however, may best be obtained by referring to the detailed description and claims when considered in connection with the drawing figures, wherein like numerals denote like elements and wherein:

FIG. **1** is a flow diagram illustrating a process in accordance with various embodiments; and

FIG. **2** illustrates a suppository in accordance with various embodiments.

DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Definitions

The term "active pharmaceutical ingredient" as used herein, means the active compound(s) used in formulating a drug product.

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of estradiol or estrone over time.

The term "bioavailability", as used herein means the concentration of an active ingredient (e.g., estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max}, and, optionally, T_{max}.